

Dissolution Kinetics of Polyvinylpyrrolidone^{1,2)}HISASHI NOGAMI, TSUNEJI NAGAI^{3a)}
and AKIRA KONDO^{3b)}*Faculty of Pharmaceutical Sciences, University of Tokyo³⁾*

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According to the rotating disk method, the dissolution of polyvinylpyrrolidone (PVP) was investigated in acetone-water system to make an approach to an understanding of general dissolution behaviors of synthetic polymers.

Three stages of dissolution were observed with the lapse of time, *i.e.*, the initial, the main, and the final stages. The initial stage disappeared upon addition of NaCl in bulk solution.

Only the main stage was explained according to Noyes-Nernst equation, and the activation energy of dissolution was close to the data reported for the diffusion controlled dissolution.

The initial stage is considered to be concerned with the swelling process of PVP inducing the dissolution, and the final stage may be concerned with the coacervation of PVP.

When NaCl was added in bulk solution, the initial stage seemed unessential for the dissolution of PVP, while the whole dissolution rate decreased. This was considered due to a suppression of the swelling of PVP on the surface of disk by the adsorption of Na⁺ on PVP.

Various kinds of synthetic polymers have been available as additives in pharmaceutical solutions or solid preparations. When they are used in the solid state, such as coating film, their dissolutions have influence on the drug release, being important upon appearance of the medicinal effect. However, kinetical investigations of the dissolution of such polymers have scarcely been made, though many works have been reported on dissolution kinetics of organic medicinals.⁴⁻⁶⁾

In the present paper, following the rotating disk method,⁵⁾ the dissolution of polyvinylpyrrolidone (PVP), one of the most popular and interesting synthetic polymers not only in pharmaceutical but in physicochemical field, was investigated in acetone-water system to make an approach to an understanding of general dissolution behaviors of synthetic polymers. As a result, three stages of dissolution were observed with the lapse of time, *i.e.*, the initial, the main and the final stages.

Experimental

Materials—Polyvinylpyrrolidone (PVP) marketed as "PVP-K30" by Gokyo Sangyo Co., Ltd. was used without further treatment. Its mean molecular weight was estimated from viscosity as 3.6×10^4

- 1) This paper forms Part XI of "Physico-chemical Approach to Biopharmaceutical Phenomena." Preceding paper, Part X: S. Wada, T. Nagai, H. Nogami, and S. Tomioka, *Yakuzaigaku*, **30**, 26 (1970).
- 2) A part of this work was presented at the 89th Annual Meeting of the Pharmaceutical Society of Japan, Nagoya, April 1969.
- 3) Location: *Hongo, Tokyo*; a) To whom communications should be directed; b) Fellow from *Pharmaceutical Research Laboratory, Kyowa Hakko Co., Ltd., Fuji Plant, Nagaizumi-machi, Shunto-gun, Shizuoka*.
- 4) a) E. Sheftner and T. Higuchi, *J. Pharm. Sci.*, **52**, 781 (1965); b) G. Millosovich, *J. Pharm. Sci.*, **53**, 484 (1964); c) D.E. Wurster and P.W. Taylor, *J. Pharm. Sci.*, **54**, 670 (1965).
- 5) H. Nogami, T. Nagai, and A. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **14**, 329 (1966).
- 6) a) H. Nogami, T. Nagai, E. Fukuoka, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), **17**, 23 (1969); b) H. Nogami, T. Nagai, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), **17**, 499 (1969).

according to the equation⁷⁾: $[\eta] = 1.4 \times 10^{-4} \times M^{0.7}$ where $[\eta]$ and M are the intrinsic viscosity at 25° and the molecular weight, respectively.

Apparatus and Procedure—Rotating disk method as described in the previous paper⁵⁾ was employed. Experiments were carried out under the following conditions: 200 ml of acetone-water (4:1)⁸⁾ at 10°, 15°, 20°, 25°; the rotating velocity of disk at 300 rpm; the disk of 2 cm diameter compressed under 5 ton/cm²⁹⁾, its density being 1.091 g/cm³. At an appropriate interval, 2.0 ml of the solution was sampled out, the resultant want being made up by adding the same amount of acetone-water (4:1) of the same temperature.

Quantitative Determination of the Dissolved Amount of PVP—After acetone in the sample was removed by heating, water was added to make 20 ml and the concentration of PVP was determined according to ultraviolet (UV) absorption method, using a Hitachi Perkin-Elmer 139 UV-VS spectrophotometer at 205 m μ . The optical density was recognized to follow Lambert-Beer rule at 195 m μ , 205 m μ , 210 m μ and 220 m μ , as shown in Fig. 1.

Results and Discussion

Acetone-water (4:1) was employed as the experimental solvent from the following reasons:

1) It was difficult to follow the progress of dissolution of polyvinylpyrrolidone (PVP) in plain water because PVP is very soluble in water; 2) Acetone is usually employed as the poor solvent for coacervation in preparing of microcapsules; 3) In the mixing ratio 4:1 of acetone-water, PVP took a coacervation at its definite concentration with a good reproducibility under such a condition as containing NaCl in the solution, as the separation in two layers was observed with addition of methylene blue. The concentration in which PVP takes a coacervation is called "coacervation concentration, C_c ," for convenience in this paper.

Dissolution Curve of Polyvinylpyrrolidone (PVP) in Acetone-Water (4:1)

The dissolution curve of PVP was formed of three stages, as shown by A (initial), B (main), and C (final) in Fig. 2. This type of curve was not observed in the cases of low molecular weight compounds.^{5,6)} From the shape of the curve, it is expected that the initial and the final stages are not interpreted by the diffusion mechanism.

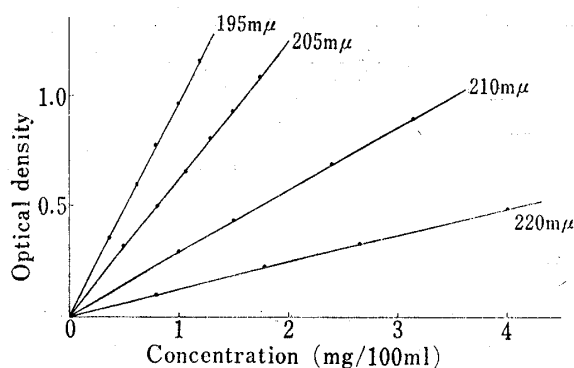


Fig. 1. Plots of Optical Density against Concentration of PVP at Various Wave Lengths

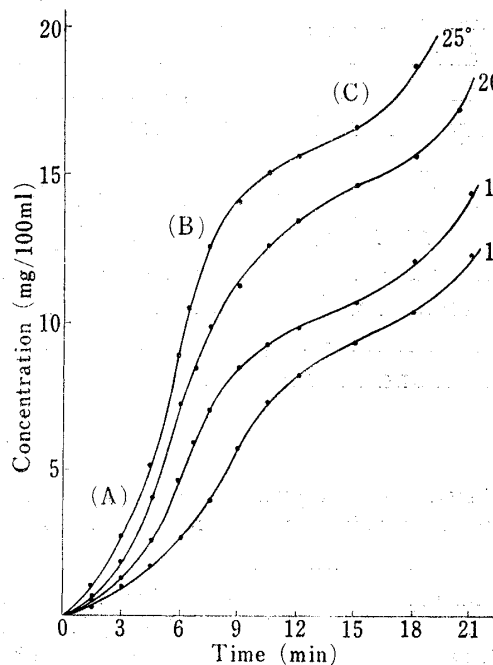


Fig. 2. Dissolution of PVP in 200 ml of Acetone-Water (4:1) at Various Temperatures from a Disk of 2 cm Diameter Rotating at a Velocity of 300 rpm

7) W. Scholton, *Makromol. Chem.*, 7, 209 (1952).

8) Mixed by the volume to volume ratio.

9) This compressional pressure was preliminarily examined to be enough to give reproducible results.

Following the method described in the previous paper,⁵⁾ the above dissolution curve was analyzed according to Noyes-Nernst equation (1).

$$\frac{dc}{dt} = k(C_0 - C) = \frac{S}{V} K_r (C_0 - C) = \frac{S}{V} \frac{D}{\delta} (C_0 - C) \tag{1}$$

where C is the concentration at the time t , C_0 the saturated concentration, k the rate constant, S the surface area of solid (disk), V the volume of solution, K_r the dissolution rate constant, D the diffusion constant, and δ the diffusion layer thickness.

Form the integrated form of equatin (1), the following equations are obtained.

$$C_2 = \exp(-k \cdot \Delta t) C_1 + \{1 - \exp(-k \cdot \Delta t)\} C_0 \tag{2}$$

$$\ln(C_2 - C_1) = -k t_1 + \ln[\{1 - \exp(-k \cdot \Delta t)\} C_0] \tag{3}$$

where C_1 is the concentration at the time t_1 and C_2 the concentration after a given time Δt , *i.e.*, at the time $(t_1 + \Delta t)$.

When Δt is maintained constant, C_2 at the respective C_1 is obtained from the dissolution curve, and if the dissolution rate is of the first order, the plot of C_2 against C_1 gives a straight line and also the plot of $\ln(C_2 - C_1)$ against t_1 gives a straight line. As was discussed,⁵⁾ equation (2) is suitable for getting the saturated concentration, C_0 from the intersection between the plot of C_2 against C_1 and the line of $C_2 = C_1$, and equation (3) is suitable for getting the rate constant, k from the slope of the plot of $\ln(C_2 - C_1)$ against t_1 .

Fig. 3 and 4 show the plots of C_2 against C_1 and of $\ln(C_2 - C_1)$ against t_1 , respectively, which consist of the three parts. If the dissolution rate follows equation (1), the slope of the plot of C_2 against C_1 should be less than unity. Therefore, only the main stage (B in Fig. 2,3 and 4) was considered to follow equation (1), *i.e.*, diffusion controlled mechanism.

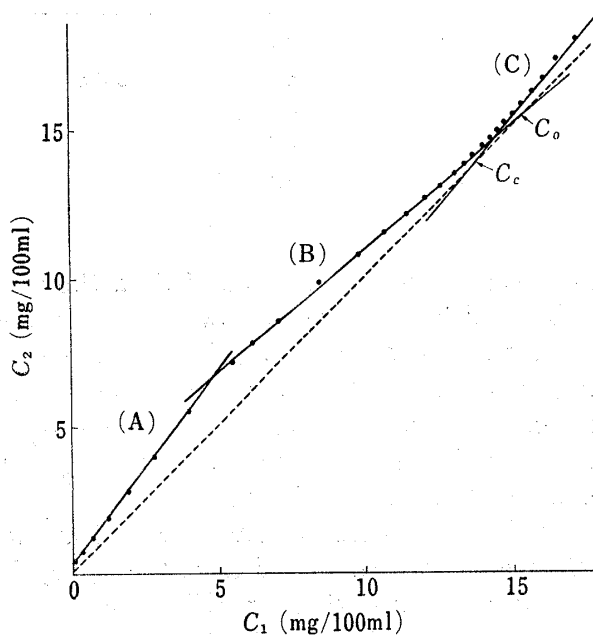


Fig. 3. Finite Differences Diagram of the Dissolution of PVP in 200 ml of Acetone-Water (4:1) at 20° from a Disk of 2 cm Diameter Rotating at a Velocity of 300 rpm

C_1 : concentration at time t_1
 C_2 : concentration at time $t_2 = t_1 + 45$ min
 ---: $C_1 = C_2$

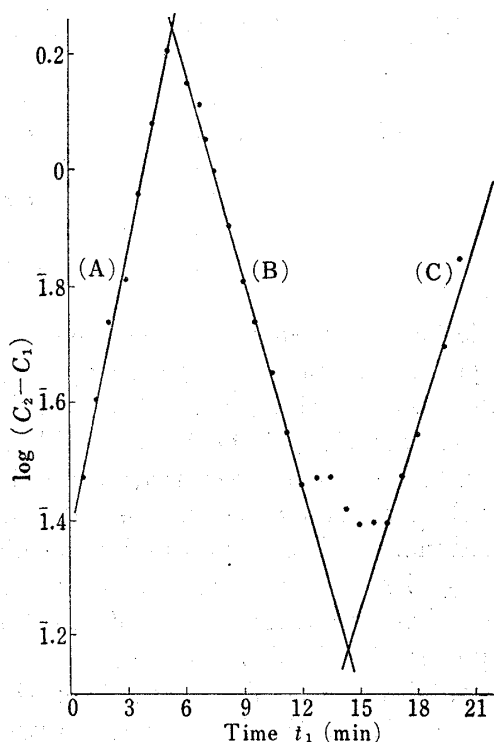


Fig. 4. Plots of $\log(C_2 - C_1)$ against Time of the Dissolution of PVP in 200 ml of Acetone-Water (4:1) at 20° from a Disk of 2 cm Diameter Rotating at a Velocity of 300 rpm

C_1 : concentration at time t_1
 C_2 : concentration at time $t_2 = t_1 + 45$ min

Discussions of the Three Stages of Dissolution of PVP

Main Stage—As mentioned above, only the main stage of the dissolution was considered to be described by Noyes–Nernst equation. However, there was observed no intersection between the plot of C_2 against C_1 and the $C_2=C_1$, and thus the values of C_0 , which are shown in Tables I and II, were estimated by extrapolating the plot to the line of $C_2=C_1$. In other words, the main stage of dissolution transferred to the final stage (C) without taking the saturated concentration, C_0 . Actually, an opalescence was observed with the naked eye around the concentration (C_c) where the main stage transferred to the final one, *i.e.*, around

TABLE I. Rate Constant, k , Dissolution Rate Constant, K_T , Saturated Concentration, C_0 , and Activation Energy of Dissolution, E_a of Main Stage (B) of PVP in 200 ml of Acetone–Water (4:1) from a Disk of 2 cm Diameter Rotating at a Velocity of 300 rpm

Temperature	$k \times 10^2$ (min^{-1})	K_T (cm/min)	C_0 (mg/100 ml)	E_a (cal/mole)
10°	8.50	5.41	9.55	3204
15°	10.6	6.76	10.6	
20°	13.5	8.60	14.4	
25°	17.3	11.4	15.8	

TABLE II. Rate Constant, k , Dissolution Rate Constant, K_T , Saturated Concentration, C_0 , and Activation Energy of Dissolution, E_a of Main Stage (B) of PVP in 200 ml of Acetone–Water (4:1) Containing NaCl from a Disk of 2 cm Diameter Rotating at a Velocity of 300 rpm

Concentration of NaCl (M)	Temperature	$k \times 10^2$ (min^{-1})	K_T (cm/min)	C_0 (mg/100 ml)	E_a (cal/mole)
0.05	10°	5.33	2.97	6.0	3506
	15°	6.33	4.03	6.4	
	20°	7.83	4.99	6.6	
0.10	10°	6.83	4.35	4.1	2980
	15°	8.33	5.30	4.5	
	20°	10.3	6.58	4.7	

a little lower concentration than the intersection point of both parts B and C on the plot of C_2 against C_1 . Such an opalescence was not observed in the cases of low molecular weight compounds.^{5,6} Here, it was disclosed that the saturation concentration, C_0 and the coacervation concentration, C_c , both obtained kinetically, are not coincident with each other, as shown in Fig. 3. A possible explanation for this difference may be given on the consideration that the polymer has a molecular weight distribution and thus the obtained values of C_0 and C_c depend more on low and on high molecular weight fractions, respectively.

Fig. 5 shows the temperature dependence of dissolution rate constant, K_T of the main stage. The activation energy of dissolution, E_a , which was calculated from the slope of the straight line in Fig. 5, was close to the data reported for the diffusion controlled dissolution.^{5,6}

Initial Stage—The part A is on the respective straight lines in Fig. 3. and 4, as it looks like a reaction of the first order. However, any theoretical equation to express the kinetics in such a stage has never been given.

Generally, the dissolution of polymer is considered to be a process of infinite swelling.¹⁰ Therefore, the initial stage in this case may be concerned with the swelling process of PVP

10) for example, a) J.H. Hildebrand and R.L. Scott, "The Solubility of Non-electrolyte," Reinhold, 1950; b) P.L. Flory, "Principles of Polymer Chemistry," Cornell Univ. Press, 1953.

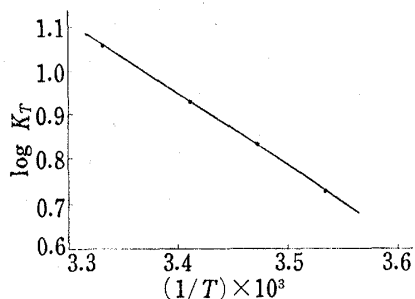


Fig. 5. Temperature Dependence of the Dissolution Rate Constant, K_T of Main Stage (B) of PVP in Acetone-Water (4:1) from a Disk Rotating at a Velocity of 300 rpm

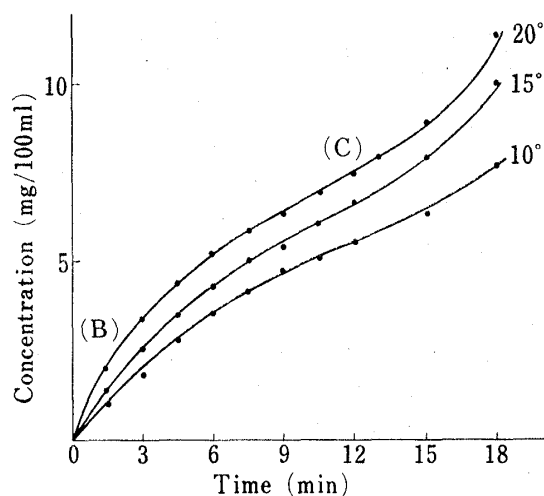


Fig. 6. Dissolution of PVP in 200 ml of Acetone-Water (4:1) Containing 0.05M NaCl at Various Temperatures from a Disk of 2 cm Diameter Rotating at a Velocity of 300 rpm

inducing the dissolution, that is, the induction stage to reach the steady state for dissolution. This stage disappeared upon addition of NaCl in the solution, as will be discussed later.

Final Stage—The part C also is on the respective straight lines in Fig. 3 and 4. However, any theoretical equation to express the kinetics has never been given.

As described already, an opalescence was observed around the concentration (C_c) where the main stage of dissolution transferred to the final one. Therefore, the final stage is considered to be concerned with the coacervation of PVP.¹¹⁾ PVP may dissolve into the saturated solution of the coacervation concentration, C_c , and the resultant excess amount of PVP is transferred to the coacervate.

It is concluded that the initial and the final stages are characteristic of the dissolution of PVP, and this may be general for many kinds of polymers. Therefore, both stages seem interesting enough to be kinetically investigated further, though they consist of much complicated heterogeneous reactions.

Effect of NaCl on the Dissolution of PVP

A pharmaceutical preparation has to come in contact with electrolytic environment when it is administered, and influences of electrolyte on various behaviors of polymer in solution have been reported.

Fig. 6 shows the dissolution curves of PVP in acetone-water (4:1) containing NaCl. A remarkable effect of NaCl was that the initial stage (part A) was lost from the curve. A possible explanation for this fact is given as follows. It has been reported that the molecule of PVP is charged with the negative¹²⁾ and water or ion is adsorbed on that molecule electrostatically according to Schulze-Hardy rule.¹³⁾ Therefore, Na^+ is considered to be adsorbed on the surface of PVP disk upon addition of NaCl in the solution, and the resultant Donnan's membrane equilibrium suppresses water molecule to penetrate into the PVP disk,¹⁴⁾ resulting in a suppression of the swelling of PVP on the surface of disk. Even if the swelling of PVP takes place in a certain degree on the surface, since the molecule of PVP takes a compact

11) B. Sébille and J. Néel, *J. Chem. Phys.*, **60**, 475 (1963).

12) L.E. Miller and F.A. Hamm, *J. Phys. Chem.*, **57**, 110 (1953).

13) a) J. Eliassaf, F. Ericksson, and F.R. Firich, *J. Polymer Sci.*, **47**, 193 (1960); b) M. Sugiura, *Kogyo Kagaku Zasshi*, **67**, 1941 (1964).

14) W. Kuhn and B. Hargitay, *Z. Electrochem*, **55**, 490 (1951).

conformation upon adsorption of Na^+ ,¹⁵⁾ the rate of diffusion of PVP may increase to result in a diffusion controlled dissolution, as is related with the increase of dissolution rate constant, K_T with the increase of concentration of NaCl, as shown in Table II. However, the values of K_T in Table I, *i.e.*, in the cases without NaCl, were larger than those in cases containing 0.05M NaCl in Table II. This is explained on the consideration that the effective surface area (or part) of PVP disk for its dissolution was enlarged by the swelling in the former case, resulting in larger observed values of K_T . Accordingly, when NaCl was added, the initial stage was considered to be unessential for the dissolution of PVP, while the whole dissolution rate decreased.

By the same circumstances as described above, the saturated concentration, C_0 was considered to decrease with the increase of NaCl, as shown in Table II, being due to the decrease in the entropy of solution of PVP.

15) a) P. Molyneux and H.P. Frank, *J. Am. Chem. Soc.*, **83**, 3169 (1961); b) P. Molyneux and H.P. Frank, *J. Am. Chem. Soc.*, **83**, 3175 (1961); c) H.P. Frank and F.R. Firich, *J. Phys. Chem.*, **61**, 1375 (1957).